STUDIES IN THE TREATMENT OF MALARIA

XV. A FACTOR HITHERTO OVERLOOKED IN THE ESTIMATION OF THE CURATIVE VALUE OF TREATMENTS OF MALARIA

BY

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We consider it desirable to commence by re-stating the procedure to which we have strictly adhered throughout the whole of our work on the treatment of malaria, and by re-defining certain terms used by us in this paper which deals solely with simple tertian malaria.

(*a*) No treatment was commenced before a microscopical diagnosis was made.

(*b*) Blood examinations were with rare exceptions made daily after completion of treatment.

(*c*) The relapses referred to in our work are without exception parasitic relapses. Febrile attacks unaccompanied by parasites in the blood within two to three days are not included, as the nature of these is unknown.

(*d*) The term 'cure' is used by us throughout this paper to signify no parasitic relapse within an observation period of sixty days,* after cessation of treatment: the observation period implying, as stated above, a *daily blood examination* after the cessation of treatment.

* This is, of course, purely an arbitrary period determined by the conditions under which we are working.

Estimation of curative value of different treatments

Consideration should convince anyone that for this purpose a post-treatment observation period is essential; blood examinations should be made as frequently as possible, for it is only by this means that malaria can be diagnosed with certainty. If the observation periods for all the cases in the different treatments are the same, then the results of these treatments are strictly comparable. If in certain treatments some of the cases are lost sight of before expiration of the maximum observation period, then in estimating the curative value of these treatments two figures must be given: (1) the number of relapses actually observed; this represents the minimum number of relapses. (2) the number of relapses actually observed plus the number of cases lost sight of before expiration of the full observation period; this represents the maximum number of relapses. For example, of the three treatments compared in Table I it is impossible to say whether Treatments I and II are better than III. It is fallacious to state that Treatment I is better than the others because only ten cases were known to relapse, as eighty cases were lost sight of, and may have relapsed, before completion of the full observation period of sixty days. Errors of this kind abound in the literature.

Table I.

Example of correct method of recording relapses.

Treatments	Number of cases treated	Number of cases which relapsed	Number of cases not relapsing but lost sight of before the expiration of 60 days	Number of cases not relapsing in an observation period of 60 days	Relapses
I.	100	10	80	10	10-90
II.	100	30	30	40	30-60
III.	100	50	0	50	50

We recorded (1918[1]) the results of treatment of seventy-six cases of simple tertian malaria by the administration of grains 90 of quinine sulphate in solution on each of two consecutive days only.

Subsequently (1918[2]) we recorded a second series of eighty-nine cases treated in the same way. Table II shews the number of cures obtained in each series.

Table II.

Treatment	Number of cases treated	Number of cases which relapsed	Number of cases not relapsing but lost sight of before the expiration of 60 days	Number of cases not relapsing in an observation period of 60 days	Cures	
					Max.	Min.
Series I	76	29	4	43	62 %	57 %
Series II	89	84	2	3	6 %	3 %

We propose to consider in this paper the factors which may explain the remarkable discrepancy between these results.

Factor 1. The number of the cases

What is the error that must be allowed for in comparing the results of observations based upon groups of seventy-six and eighty-nine cases respectively? Taking the error as approximately proportional to the square root of the number of cases observed, the corrected values would be for:—

Series I ... ... 46 to 68 per cent. of cures.
Series II ... ... 0 to 16 „ „

or by applying Poisson's formula*:

Series I ... ... 41 to 73 per cent. of cures.
Series II ... ... 0 to 13 „ „

The figures do not overlap.

Conclusion: This factor cannot explain the discrepancy.

Factor 2. The quinine solution and mode of administration

The quinine solution was identical in both series, viz.: Howard's, and an analysis of the solutions used in the two series showed that the strength was correct. As regards mode of administration there was a slight difference in the two series, inasmuch as eighteen of the seventy-six cases of Series I had some portion of the (grains 180) dose of quinine given intramuscularly.

* This formula for estimating liability to error is: $\frac{m}{\mu} \pm 2\sqrt{\frac{2mn}{\mu^3}}$. In this case m = percentage of cures, n = percentage of relapses, μ = total cases.

If, however, we compare the fifty-eight cases of Series I with the eighty-nine of Series II, in which the mode of administration was entirely by the mouth, we get 63 per cent. of cures for the first series and 6 per cent. for the second.

Conclusion: This factor cannot explain the discrepancy.

Factor 3. Strain of Parasite

In Series I practically all the cases (seventy-two of seventy-six) were infected in Salonika. In Series II thirty-nine were infected in Salonika, forty-three in E. Africa.

Table III.

Factor 3: Strain of parasite.

Treatment	Salonika		E. Africa	
	Cases	Cures	Cases	Cures
Series I	72	65%	...	...
Series II	39	3%	43	7%

Table III shows:—

(*a*) That in the second series of observations the percentage of cures is practically the same whether the cases were infected in Salonika or E. Africa.

(*b*) That amongst the Salonika cases 65 per cent. of the first series were cured, but only 3 per cent. of the second series.

Conclusion: This factor cannot explain the discrepancy.

Factor 4. Length of time between date of infection and treatments under discussion

The date of infection cannot be determined with exactitude, but we have been able to ascertain:—

A. The length of time between first reporting sick for malaria and the treatments.

TABLE IV.

Factor 4A: Length of time between first reporting sick and the treatments.

Treatment	0-12 months		13 months upwards	
	Cases	Cures	Cases	Cures
Series I	23	57%	23	74%
Series II	53	2%	36	8%

Table IV shows:—

(*a*) That in both the first and second series of observations there is not much difference in the percentage of cures whether the length of time since first reporting sick is under twelve months or over twelve months.

(*b*) That of the cases in which the length of time since first reporting sick is under twelve months the percentage of cures is much greater in Series I than in Series II; this applies also to the cases in which the length of time since first reporting sick is over twelve months.

B. Length of time between leaving the infected area and date of treatments.

TABLE V.

Factor 4B: Length of time between leaving infected area and date of treatments.

Treatment	0-9 months		10 months upwards	
	Cases	Cures	Cases	Cures
Series I	18	61%	20	75%
Series II	64	3%	...	...

Table V shows:—

(*a*) That in the first series of observations there is not much difference in the percentage of cures obtained, whether the length of time since leaving the infected area is under nine months or over nine months.

(*b*) That among the cases which had left the infected area for a period of less than nine months the percentage of cures is much greater in Series I than in Series II.

Conclusion: This factor cannot explain the discrepancy.

Factor 5. Length of time between arrival in England and treatments under discussion

TABLE VI.

Factor 5: Length of time between date of arrival in England and the treatments.

Treatment	0-6 months		7 months upwards	
	Cases	Cures	Cases	Cures
Series I	24	71%	17	65%
Series II	64	5%	...	...

Table VI shows:—

(*a*) That in the first series of observations there is not much difference in the percentage of cures whether the cases have been in England under six months or over six months.

(*b*) That of the cases which have been less than six months in England the percentage of cures obtained is much greater in Series I than in Series II.

Conclusion: This factor cannot explain the discrepancy.

Factor 6. Time of year at which treatment was administered

TABLE VII.

Factor 6: Time of year at which treatment was administered.

Treatment	Date	Cases	Cures	
			Maximum	Minimum
Series I	July-Sept., '17	76	62%	57%
Series II	Jan.-Apr., '18	89	6%	3%

Table VIII.

Shewing the Monthly (and Quarterly) percentage of Cures* obtained from February, 1917 to April, 1918.

Nature and Duration of Treatment	1917 Feb. R †C	Mar. R C	Apl. R C	May R C	June R C	July R C	Aug. R C	Sept. R C	Oct. R C	Nov. R C	Dec. R C	1918 Jan. R C	Feb. R C	Mar. R C	Apl. R C	May R C
Quinine bihydrochloride, grs. 15 intramuscularly on each of 2 consecutive days	5 0	14 1	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Quinine bihydrochloride, grs. 10-15 intravenously (single injection)	1 0	5 0	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Quinine bihydrochloride, grs. 10-15 intravenously thrice weekly for 2 weeks	6 0	6 1	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Quinine sulphate, grs. 15 orally on each of 2 consecutive days	...	2 0	12 0	...	...	...	...	...	...	...	...	...	...	...	...	...
Quinine sulphate, grs. 10 orally on each of 2 consecutive days	...	...	10 0	...	...	...	...	...	...	...	...	...	...	...	...	...
Quinine bihydrochloride, grs. 5 orally on each of 2 consecutive days	...	...	10 0	8 0	...	...	...	...	...	...	...	...	...	...	...	...
Quinine sulphate, grs. 30 orally on each of 2 consecutive days	...	...	...	14 0	...	...	...	...	...	...	...	...	...	...	...	...
Quinine sulphate, grs. 45 orally on each of 2 consecutive days	...	...	...	9 3	...	...	...	...	...	...	...	...	...	...	...	...
Quinine sulphate, grs. 30 orally daily for 8 weeks	...	...	...	24 5	...	...	...	...	...	...	...	...	...	...	...	...
Quinine sulphate, grs. 30 orally daily for 3 weeks, and grs. 45 orally daily for 1 week	...	...	...	17 5	...	...	...	...	...	...	...	...	...	...	...	...
Quinine alkaloid, grs. 15-60 intramuscularly (either 1 or 2 injections)	...	...	...	12 3	19 4	...	...	...	...	...	...	...	...	...	...	...
Quinine sulphate, grs. 30 orally daily for 5-18 weeks	...	...	...	6 0	3 3	1 1	...	...	...	...	...	...	...	...	...	...
Quinine sulphate, grs. 5 orally on each of 2 consecutive days	...	...	...	...	11 1	...	...	...	...	...	...	...	...	...	...	...
Quinine sulphate, grs. 60 orally on each of 2 consecutive days	...	...	...	...	7 5	...	...	...	...	...	...	...	...	...	...	...
Quinine sulphate, grs. 20 orally daily for 14-15 weeks	...	...	...	...	3 2	...	...	...	...	...	...	...	...	...	...	...
Quinine sulphate, grs. 45 orally daily for 3-8 weeks	...	...	...	...	7 10	0 2	...	...	...	...	...	...	...	...	...	...
Quinine sulphate, grs. 45 orally on 2 consecutive days weekly for 8 weeks	...	...	...	...	5 8	1 7	...	...	...	...	...	...	...	...	...	...
Quinine sulphate, grs. 90 orally on each of 2 consecutive days (1st series)	...	...	...	...	...	10 8	11 23	8 16	...	...	...	...	...	...	...	...
Quinine sulphate, grs. 10 orally on 2 consecutive days weekly for 8-16 weeks	...	...	...	...	...	5 9	1 1	1 0	...	...	...	...	...	...	...	...
Quinine sulphate, grs. 90 orally on 2 consecutive days weekly for 3 weeks	...	...	...	...	...	0 1	0 2	1 2	9 5	1 2	0 1	...	...	...	...	...
Quinine sulphate, grs. 120 orally on each of 2 consecutive days	...	...	...	...	...	...	...	4 3	5 3	...	...	...	...	...	...	...
Novarsenobillon, gm. 0·4, single intravenous injection	...	...	...	...	...	...	...	...	...	5 1	4 1	3 0	3 0	...	...	...
Quinine sulphate, grs. 90 orally on each of 2 consecutive days (2nd series)	...	...	...	...	...	...	...	...	...	...	...	2 0	8 0	41 2	32 4	...
Novarsenobillon, gm. 0·6, single intravenous injection	...	...	...	...	...	...	...	...	...	...	...	...	5 0	16 1	...	...
Novarsenobillon, gm. 0·9, single intravenous injection	...	...	...	...	...	...	...	...	...	...	...	...	...	...	9 0	8 3
C17. Quinine bihydrochloride, grs. 30 intramuscularly, and quinine hydrochloride, grs. 30 orally daily for 12 days	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	25 5
Totals	12 0	27 2	32 0	90 16	55 33	17 28	12 26	14 21	14 8	6 3	4 2	5 0	16 0	57 3	41 4	33 8
Percentage of cures each month	0	7%	0	15%	37%	62%	68%	60%	36%	33%	33%	0	0	5%	9%	19·5%
Percentage of cures each quarter	5%		21·7%			63·6%			35·2%			3·7%				

* By 'Cure' is meant no parasitic relapse within a post-treatment observation period of 60 days. † R = Relapses. C = Cures.

Table VII shows that whilst the first series of cases were treated in July, August and September, 1917, the second series were treated in January, February, March and April, 1918.

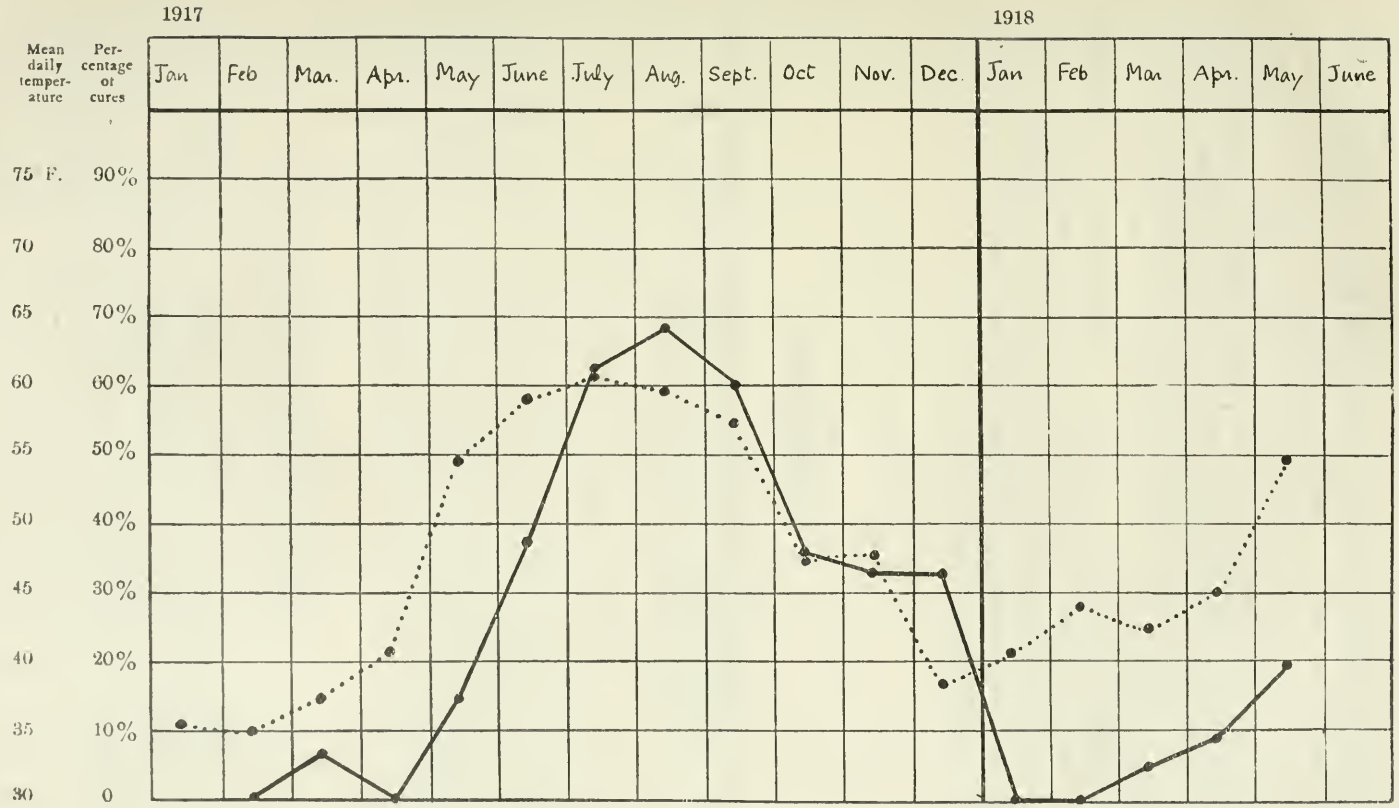
Conclusion: This factor may possibly explain the discrepancy.

We proceeded, therefore, to enquire whether the data in our possession supported this explanation. In Table VIII we have arranged all the cases treated by us during the last seventeen months, irrespective of the nature of the treatment to which they were submitted, according to the month in which the treatment ended. In each vertical column the number of relapses and of cures among the cases completing treatment in each month are given, and at the foot of each column is the monthly percentage of cures obtained; in addition the percentages of cures for each quarter of the year are recorded. The data are also shown in Graph 1.

It will be seen that Graph 1, which represents the percentage of cures obtained, varies with the month of the year in which the treatment ended; broadly speaking, a very small percentage of cures is obtained in the winter and spring and a comparatively high percentage in the summer and autumn. These facts, then, support the hypothesis that the discrepancy between the results obtained in the first and second series of treatments, by quinine grains 90 on each of two consecutive days, is due to the different periods of the year at which the treatments were administered.

With a view to examining this question more fully, we have obtained the meteorological observations made at the Liverpool Observatory from January, 1917, to May, 1918, and so far as we can see, the only meteorological factors that are in any way correlated with the seasonal variation in the percentage of cures obtained by us are the variations in the mean temperature, and prevalence of the east wind. The average mean daily temperature for each month during the period January, 1917, to May, 1918, is given in Graph 2. It will be seen that the general form of this agrees with that of Graph 1 representing the monthly percentage of cures effected by our treatments. The higher the mean daily temperature the higher the percentage of cures.

These observations apply to England. We are unable to say whether or not they have any application to other countries where the seasons are different or to climates in which the



Graph 1 : Percentage of cures

Graph 2 : Mean daily temperature

meteorological conditions are not comparable. Our data are also at present insufficient to show whether the more favourable results obtained by treatments carried out during the summer were due to the occurrence of actual cures, or only to a prolongation of the period of latency. We are also at present unable to say if treatments with smaller doses of quinine than grains 90 on two consecutive days would or would not be equally effective if administered during the summer months.

Whether or no we are correct in our conclusion that the season at which treatment for malaria is given influences the results obtained, there seems to be no doubt that we must recognise the fact that the same treatment if carried out on different occasions may give quite dissimilar results.

REFERENCES

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